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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/845,416	Applicant(s) XIAO, XIAO
	Examiner Brian Whiteman	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *10*.

DETAILED ACTION

Non-Final Rejection

Claims 1-17 and 24-28 are pending examination.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that Group II is included within Group I since Group I encompasses Group II. See pages 1-2. The traversal is found partially persuasive and Group II will be rejoined with Group I. However, the applicants have not provided sufficient reason to overcome the restriction between Group I and Group III set forth in the election restriction paper no. 8.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Note: If the products claims are novel then the method claims will be rejoined with the product claims.

Information Disclosure Statement

The information disclosure statement filed 2/25/02 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. patent, which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the US Patents referred to therein has not been considered.

The international search report PCT/US01/13677 has been considered.

Specification

The disclosure is objected to because of the following informalities: the specification has duplicate copies of the claims, see pages 27-31 of the specification.

Appropriate correction is required.

Claim Objections

Claim 2 is objected to for reciting a grammatically improper phase, "comprising a last three amino acids of a C-terminal domain....." Amending the claims to recite ".....comprising the last three amino acids of a C-terminal domain.....," would obviate this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 and 24-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) An isolated nucleotide sequence encoding a dystrophin mini-gene comprising: a) a N-terminal domain; b) four to six rod repeats; c) the H1 domain of the dystrophin gene and the H4 domain of the dystrophin gene; and d) a cysteine-rich domain, wherein the N-terminal domain is selected from a group consisting of the N-terminal domain of the dystrophin gene or the N-terminal domain of a utrophin gene; the rod repeats are selected from a group consisting of the rod repeats in the dystrophin gene, the rod repeats in the utrophin gene, and the rod repeats in a spectrin gene; the cysteine-rich domain is the cysteine-rich domain

of the dystrophin gene or the cysteine-rich domain of the utrophin gene; 2) An isolated nucleotide sequence encoding a dystrophin mini-gene comprising: a) the N-terminal domain of the dystrophin gene; b) four to six rod repeats of the dystrophin gene; c) the H1 domain of the dystrophin gene and the H4 domain of the dystrophin gene; and d) a cysteine-rich domain, wherein said nucleotide sequence has fewer than 5,000 nucleotides; 3) A recombinant adeno-associated virus vector comprising the nucleotide sequence of 1, wherein the sequence is operably linked to an expression control element; 4) A recombinant adeno-associated virus vector comprising the nucleotide sequence of 2, wherein the sequence is operably linked to an expression control element; and does not reasonably provide enablement for the full scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is a dystrophin mini-gene that harbors biological functions that can protect the muscle from dystrophin pathology and symptoms. The field of the invention lies in producing recombinant DNA sequences with dystrophin activity.

At the time the application was filed, predicting any protein tertiary structure based on a protein structure was considered to be unpredictable due to significant problems in several areas. The state of the art, exemplified by Chiu et al., *Folding and Design*, Vol. 3, pg. 223-228, May 1998, displays major consideration for predicting a protein tertiary structure involve issues that include:

Predicting the three-dimensional conformation of a correctly folded protein can be divided into two distinct steps: the construction of a fitness function to evaluate the various conformations: and the search through various possible conformations for the "best" prediction most likely to represent the native state. Neither part of this problem has proven particularly tractable. The development of a general method for the prediction of protein tertiary structure based on the protein sequence remains, unfortunately, one of the great-unsolved problems of computational biophysics (pg. 223).

The specification teaches that the mini-gene comprises the N-terminus sequence of the dystrophin gene, the C-terminal Cysteine-rich (CR) domain of the dystrophin gene, at least H1 and H4 hinges of dystrophin gene, and at least four rod repeats (page 14). The rod repeats may be chosen from the rod repeats of dystrophin, utrophin, spectrin genes. The N-terminus of the dystrophin mini-gene may be modified to improve expression without affecting the functionality of the gene product (page 15). The as-filed specification teaches the construction of truncated dystrophin mini-genes and AAV vectors carrying the mini-genes (See Example 1).

In view of the art of record, the as-filed specification only provides sufficient guidance for one skilled in the art to make and/or use the mini-genes listed under scope of enablement and does not provide enablement for isolated nucleotide sequences that encode other dystrophin mini-genes. The claimed invention is not enable for the full scope of the claims because the breadth of the claims encompass production of a mini-gene with a modified N-terminal, a modified H1, or a modified H4 domain. The as-filed specification uses sequences from dystrophin with specific SEQ ID NOS (see page 18). The claims recite nucleotide sequences that encode a N-terminal (e.g. modified N-terminal), a H1 and a H4 domain that has dystrophin

activity. Furthermore, the specification provides no guidance as to which of the nucleotides may be changed while dystrophin activity is retained. The state of the art further teaches that the relationship between a nucleotide sequence and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et al, The Protein Folding Problem and Tertiary Structure Prediction, 194, Merz et al (ed.), Birkhauser Boston, MA, pp. 433 and 492-492). In view of the art of record and the lack of sufficient guidance provided by the as-filed specification for the genus of modified N-terminal and/or modified H1 or H4 domains, it would take one skilled in the art an undue amount of experimentation to reasonably correlate from the working examples to the full scope of the claimed invention. Therefore, the claimed invention is only enabled for making and/or using the dystrophin mini-genes set forth in the scope of enablement.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the claimed invention encompassing 1-4, listed above. Given the state of art for predicting a tertiary structure (biological activity) based on a primary nucleotide sequence, one would have to engage in a large quantity of experimentation in order to practice the full scope of the claimed invention based on the application's disclosure, the unpredictability of the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) (Chiu et al., *Folding and Design*, 1998, pp. 223-228). In addition, the presence of a working example as provided in the specification does not extrapolate to the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 8-13 and 24-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially complementary" in claims 8-13 is a relative term, which renders the claims indefinite. The term "substantially complementary" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term. The claims do not particularly point out what percentage (1%, 20%, 50%, 99%, etc.) defines the term.

The statement in claims 24-28, "… **a** nucleotide sequence of claim (9, 10, 11, 12, or 13) …" is indefinite because it does not point out which sequence **a nucleotide sequence** is referring to in the claim. The dependent claim refers to several nucleotides, however, the claim from which the dependent claims are based on refers to one . The dependent claim should state "…. **the** nucleotide sequence of claim…".

Claim Rejections - 35 USC § 102

Note: In view of the rejection under 112 second paragraph for lack of definition for the term "substantially complementary", the following rejection for claims 8-13 and 24-28 apply:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Koenig et al. (IDS, Cell, Vol. 53:219-228, 1988). Koenig teaches the complete sequence of the human dystrophin cDNA comprising of the N-terminal domain, rod repeats, H1 and H4 domains, Cysteine rich domain, and C-terminal domain (abstract).

Claims 1-3, 5-14, 16, and 24-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Takeda (JP1999318467A, published on 11/24/99, translation in English of the Japanese document is provided). Takeda teaches production of several kinds of mini-dystrophin genes having 4.5kb or less and the gene has N-terminal, hinge 1, hinge 4, rod-repeat of various numbers, cysteine rich domain and/or C-terminal domain (See specification). Takeda further teaches using said mini-gene for producing a recombinant adeno-associated viral (rAAV) vector comprising said mini-gene for studying *in vitro* expression of gene product (See specification). Takeda teaches a rod- shortened dystrophin encoding nucleotide sequence having 4402 base pairs that is substantially complementary to the claimed nucleotide sequences. Furthermore, because the metes and bounds of the phrase "substantially complementary stand" is indefinite, the sequence taught by Takeda is 46% identical to the claimed sequence and is substantially complementary to the sequence set forth in the claims.

Suggest amending claims 8-13 to read as follows: The isolated nucleic acid sequence of claim …. , consisting of SEQ ID NO: X (2, 6, 9, 10, 12, or 14) or which is the full complement strand of SEQ ID NO: X (2, 6, 9, 10, 12, or 14).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

Claims 1, 3, 8, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takeda (JP1999318467A, 11/24/99) taken with Li et al (IDS, Gene Therapy, Vol. 6, pp. 74-82, 1999). Takeda teaches production of several kinds of mini-dystrophin genes having 4.5kb or less and the gene has N-terminal, hinge 1, hinge 4, rod-repeat of various numbers, cysteine rich domain and/or C-terminal domain (See specification). Takeda further teaches using said mini-gene for producing a recombinant adeno-associated viral (rAAV) vector comprising said mini-gene for studying *in vitro* expression of gene product (See specification). Takeda teaches a rod-shortened dystrophin encoding nucleotide sequence having 4402 base pairs that is substantially complementary to the claimed nucleotide sequences. However, Takeda does not specifically teach a rAAV comprising a mini-dystrophin gene operatively linked to a CMV promoter.

However, at the time the invention was made, Li reports efficient transduction of muscle cells using a rAAV vector comprising a nucleotide encoding a sarcoglycan protein operatively linked to a CMV promoter. Li states, "CMV promoter has been shown to exhibit elevated and sustained activity in muscle tissue in the context of rAAV" (page 75).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to use the CMV promoter in the AAV vector comprising the mini-dystrophin gene. One of ordinary skill in the art would have been motivated to use the CMV promoter because rAAV with the CMV promoter has been shown to exhibit elevated and sustained activity in muscle tissue.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
9/27/02

DAVE T. NGUYEN
PRIMARY EXAMINER